PREPARATION AND CHARACTERIZATION OF ARTESUNATE - NICOTINAMIDE COCRYSTAL BY SOLVENT EVAPORATION AND SLURRY METHOD

by Retno Sari

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Research Article

PREPARATION AND CHARACTERIZATION OF ARTESUNATE - NICOTINAMIDE COCRYSTAL BY SOLVENT EVAPORATION AND SLURRY METHOD

DWI SETYAWAN*[1], RETNO SARI[1], HELMY YUSUF[1], RIESTA PRIMAHARINASTITI[2]

[1]Department of Pharmaceutics, Airlangga University, [2]Department of Analytical Chemistry, Airlangga University.
Email: dwisetyawan_90@yahoo.com

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ABSTRACT

Objective: The present study aims to prepare and characterize cocrystals of artesunate (AR) - nicotinamide (NI) in order to improve bioavailability and efficacy of artesunate as an antimalarial drug.
Methods: Cocrystals were prepared using solvent evaporation and slurry methods. Physicochemical characterizations were performed using Hot Stage Microscope (HSM), infrared spectroscopy (IR), thermal analysis DTA, Powder X-Ray Diffraction (PXRD) and Scanning Electron Microscope (SEM).
Results: The study revealed that re-crystallization of AR, NI and a physical mixture of both compounds showed distinctive shapes as shown by HSM microscope. AR has a needle shape, whereas NI showed mosaic spherulite crystal. Furthermore, as the two compounds experienced a contact one another, new crystals i.e. fiber-like shape were observed, indicating formation of a cocrystal of AR-NI was successfully achieved. Two different molar ratios of AR-NI from the phase diagram (i.e. 50:50 and 60:40 %) showed a decrease in the melting temperature i.e. 104.0°C and 104.7°C, respectively, in comparison with the melting point of the constituent materials (AR 133.6°C and NI 142.2°C). PXRD diffractogram showed that cocrystal of AR–NI exhibited new diffraction peaks at 2θ = 5.8°; 17.4° and 17.8°, whereas no peaks were found for physical mixtures of AR - NI. Characterization with IR showed disappearance of transmission peaks at 2976 and 2639 cm^{-1} indicating a loss of NH^{3+} bending bands. Furthermore, disappearance of C=O stretch at 1346 cm^{-1} and -OH bending at 1485 cm^{-1} indicated a formation of hydrogen bonding between AR and NI. This was due to the formation of cocrystals prepared by solvent evaporation method, since the cocrystals made by the slurry method only showed the loss of NH_{3^+} at 2639 cm^{-1}. SEM micrographs showed that cocrystals prepared by solvent method have a more homogeneous mixture of AR-NI compared to the cocrystal formed by slurry method.
Conclusion: The study concludes that cocrystals of AR-NI were successfully formed using solvent evaporation and slurry methods. The formed co-crystals of AR - NI exhibited different physicochemical characteristics as compared to the constituent materials. The formed cocrystals prepared by solvent evaporation method have a lower melting point and relatively more homogeneous in terms of crystal composition.

Keywords: *characterization, artesunate, nicotinamide, cocrystal, solvent evaporation method, slurry method*

INTRODUCTION

Malaria is an infectious disease that still remains as a major health problem in many countries [1]. Conventional treatment for malaria is using a combination of multiple drugs and not specifically targets the intracellular parasites, thus requires larger doses. As consequence, the toxicity becomes less tolerable. Artemisinin derivative is one of several antimalarial drug that resistant to strains of Plasmadium falcifarum. Artesunate is one of the derivative of artemisinin which is highly potent on schizonticidal. It is classified as a class II drug in the Biopharmaceutical Classification System (BCS); poor solubility in water and low bioavailability when administered orally. This creates problems in formulation and some limitations on applications as biopharmaceutics and the efficacy [2].

Many approaches such as the use of liposomes, nanoparticles and complex formation of artesunate-β-cyclodextrin have been investigated to improve the solubility and bioavailabilty [2]. In recent years, modification such as the use of pharmaceutical cocrystals has also been investigated extensively. Cocrystal is defined as crystalline complexe of two or more neutral molecules bonded together in the crystal lattice via non-covalent interactions. One of the components includes the active pharmaceutical ingredient. Studies on cocrystal have shown an improvement of their solubility [3], dissolution rate, stability and other processes related properties [4]. Co-crystals can be designed by crystal engineering to improve the properties of pharmaceuticals without affecting the internal structure of the crystal. Methods that have been used to prepare cocrystals include solvent evaporation, milling (grinding) and super critical fluid (SCF) [3].

Nicotinamide or niacinamide is widely used as cocrystal formers. Nicotinamide as vitamin B derivative is often used because it is very safe for the use in humans. The formation of cocrystals generally involves functional groups such as amides, carboxylic acids and alcohols. Nicotinamide has an active amide group with a high electronegativity as results of the N atom silent pairing that led to a strong intermolecular hydrogen bond; which is required for the formation of cocrystals [5]. For instance, formation of cocrystals that are composed of ibuprofen - nicotinamide [4] and carbamazepin – nicotinamide [5] have been proved to improve the solubility of the active pharmaceutical ingredients.

Based on the above studies, the present studies were carried out to prepare cocrystal system composed of artesunate and nicotinamide to increase the solubility of artesunate. Physicochemical characterization were performed by Hot Stage Microscope (HSM), infrared spectroscopy (IR), thermal analysis DTA , Powder X - Ray Diffraction (PXRD) and Scanning Electron Microscope (SEM).

MATERIALS AND METHODS

Materials

Artesunate was purchased from Ancalima Lifesciences Ltd., India, bacth no. AS/M-001/07-08. Nicotinamide was purchased from Asahi Chem. Co., Kansei, Japan.

Methods

Examination of Cocrystal formation with Heat Contact

Heat contact method was performed under a polarized microscope equipped with an electric desk heater (Hot Stage). Certain amount of

artesunate was placed on glass objects, covered, heated to melt and allowed to recrystallize again. Afterwards, the nicotinamide powder was placed right on the glass cover boundary. The sample system was heated again until all the nicotinamide melts. The melting nicotinamide was allowed to move and made contact with the surface of artesunate crystal. The area of contact (contact zone) between artesunate and nicotinamide were observed for the growth of new crystals under polarizing microscope at 200x magnification. The cocrystals formation was recorded using a digital camera [6].

Preparation of Phase Diagram of Binary System

Artesunate and nicotinamide were sifted and weighed to obtain particle size in similar range. The obtained physical mixtures were obtained by simply mixing artesunate with nicotinamide at different molar ratios as follows: (30/70), (40/60), (50/50), (60/40), (70/30), respectively. The mixtures were gently mixed in a mortar for 5 minutes. The melting point of physical mixtures of artesunate - nicotinamide was determined by DTA. Endothermic peak was plotted against the molar fraction of the mixture to obtain the phase diagram of artesunate - nicotinamide .

Preparation of Artesunate – Nicotinamide Physical Mixture

Artesunate and nicotinamide (equimolar) carefully weighed; 3.15 grams and 1.0 grams, respectively. Both powders were homogeneously mixed in a mortar.

Preparation of Cocrystal Using Solvent Evaporation Method

Artesunate and nicotinamide (equimolar) carefully weighed as much as 3.15 grams and 1.0 grams respectively. Each compound was dissolved in methanol separately. Artesunate was dissolved in approximately 140 mL of methanol to form a clear solution. Nicotinamide was dissolved in approximately 15 mL of methanol. The two solutions were mixed and stirred for a few minutes. Equimolar solution of both components was evaporated at room temperature for 48 hours. The obtained cocrystal solids were stored in a desiccator under vacuum.

Preparation of Cocrystal Using Slurry Method

Artesunate and nicotinamide (equimolar) carefully weighed as much as 3.15 grams and 1.0 grams respectively. Both powders were mixed homogeneously in mortar. 15 mL of water was added to the mixture to form a slurry sample. The formed cocrystal was dried at temperature of 40°C for 48 hours. The solid cocrystal was stored in a desiccator under vacuum.

Physicochemical Characterization Cocrystals

Differential Thermal Analyzer (DTA) was used to analyze the thermal properties. The DTA (METLER Toledo FP 85, Switzerland) was calibrated with indium before analysis. Certain amount of samples i.e. 5-7 mg samples were placed in a sealed aluminum pan. The analysis was performed in a temperature range of 50 to 300°C with a heating rate of 10°C per minute.

Characterization By Powder X-Ray Diffraction Method

Powder X-ray diffraction (Phillips X'Pert diffractometer) analysis was performed at room temperature. Condition of measurement was set as follows: Cu metal target, Kα filter, voltage of 40 kV, 40 mA. The analysis was performed on the range of 2 theta of 5-40°. Sample was placed on the sample holder and flatted to prevent particle orientation during preparation.

Characterization Using Scanning Electron Microscopy (SEM)

Sample was placed on the sample holder and coated with gold aluminum with a thickness of 10 nm. The sample was then observed at various magnification using SEM instrument (JEOL, Japan) with voltage was set at 20 kV and 12 mA.

Characterization Using Fourier Transform Infrared Spectroscopy (FTIR)

Approximately 1%w/w dispersion of sample powder in potassium bromide (KBr) was prepared by mixing the sample powder with KBr. The infrared spectrum was obtained using infrared spectrophotometer (Spectrum One, Perkin Elmer) in wave length range of 400-4000 cm^{-1}.

RESULTS AND DISCUSSION

The obtained recrystallization of the melting artesunate (AR) and nicotinamide (NI) was seen in different colours as they were observed under the polarizing microscope (Figure 1). Hot Stage Microscope (HSM) Polarization was used to detect the formation of co-crystals artesunate-nicotinamide. The observed variety of colours was due to the light intensity which is influenced by the fragment orientation and thickness of the beam transmitted by the crystal fragments. Recrystallization of single AR, NI, and their mixture showed a distinctive shape. AR has a needle shape, whereas NI has spherulite mosaic crystal shape (Figure 1). The mixture of the two materials showed formation of new crystals at the contact area that exhibit different forms from the constituent materials. The new crystal was seen as a fiber-like form, indicating formation of cocrystals of AR and NI.

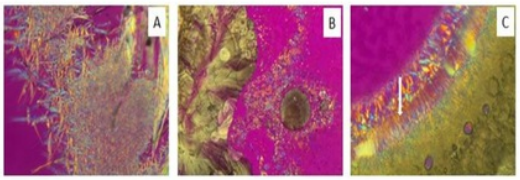

Fig 1: Crystal images obtained by Hot Stage Polarized Microscope A).AR, B). NI, and C). contact area of fused AR and NI (arrows) which was observed at 105°C.

The phase diagram of AR-NI mixture was made using different molar ratios (i.e. 100:0, 70:30, 60:40, 50:50, 40:60, 30:70 and 0:100)%. The results show that the molar ratio of 50:50 and 60:40% showed a decreased melting temperature of each component. AR melted at 133.6°C and NI melted at 142.2°C, whereas the mixture with molar ratio of 50:50 and 60:40% melted at 104.0 and 104.7°C, respectively. The decrease melting temperature of each constituent materials indicated that they formed an eutectic reaction between AR and NI at molar ratio of 50:50 and 60:40% as shown in Figure 2.

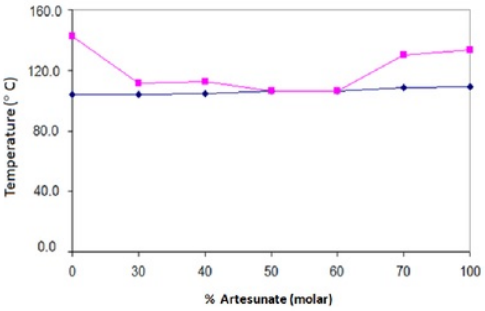

Fig 2: Phase diagram of binary system AR:NI with various compositions.

Based on these data, the cocrystal formation of artesunate-nicotinamide used molar ratio of 50:50. Cocrystal of artesunate-nicotinamide and their physical mixture were then characterized using DTA as shown in Figure 3. The results indicated that a decrease in AR and NI melting temperature as compared to the constituent materials. Cocrystal that was prepared by solvent evaporation method has a melting temperature of 96.4° C ΔH=13.0 J/g, while the cocrystal which was prepared by slurry method has a melting temperature of 98.4°C ΔH = 19.0 J/g. The melting point of their physical mixture was 106.5°C ΔH = 21.9 J/g. The decreased melting point indicated interactions between materials [7].

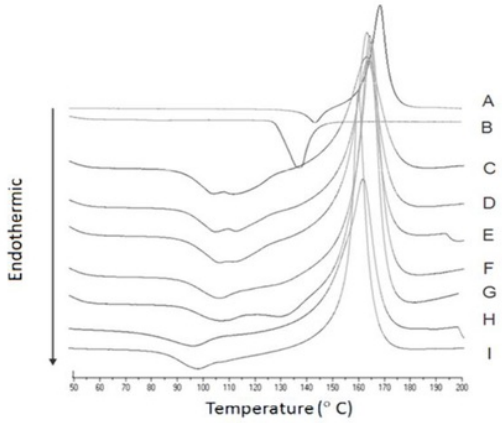

Fig. 3: DTA thermogram A. AR, B. NI, C. AR-NI physical mixture 30:70, D. AR-NI physical mixture 40:60, E. AR-NI physical mixture 50:50, F. AR-NI physical mixture 60:40, G. 70:30 AR-NI physical mixture, H.cocrystal solvent evaporation and I. cocrystal slurry method.

Figure 4 showed the PXRD diffractogram of AR, NI, physical mixture of AR-NI and cocrystals of AR and NI. AR has a specific diffractogram at 2θ = 7.7°; 9.4°; 12.9°; 15.5° and 18.6°. NI has a specific diffractogram at 2θ = 9.5°; 11.3°; 14.7°; 19.5° and 22.2°. Diffractogram of cocrystal AR-NI showed peaks at 2θ = 5.8 °; 17.4° and 17.8 ° which were not found in the diffractogram of AR and NI in their physical mixture. Diffractogram of the physical mixture was a superposition of two constituent materials. It is widely accepted that PXRD is a very reliable method to provide information of solid systems in terms of interaction between materials. Such interactions may produce new diffraction peaks as compared to the constituent materials [8,9].

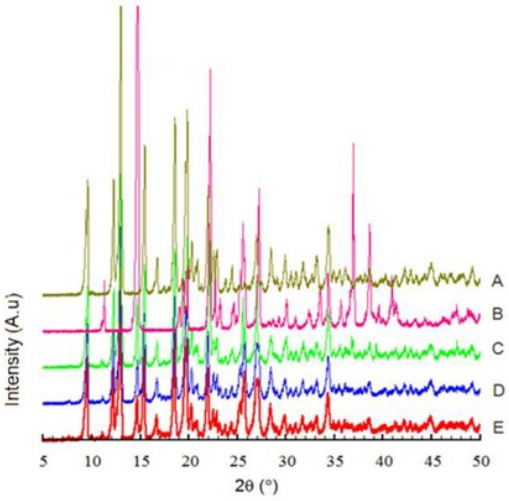

Fig.4: Powder X-ray diffractogram A. AR, B. NI, C. AR-NI physical mixture 50:50, D. cocrystal AR-NI (solven evaporation) and E. cocrystal AR-NI (slurry method).

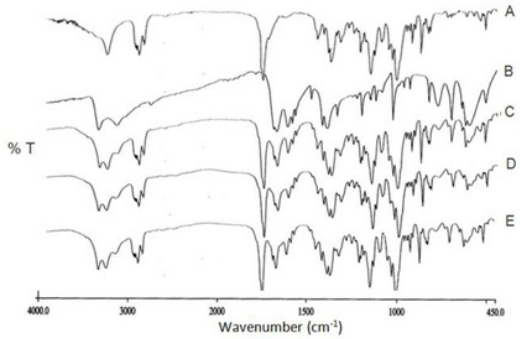

Fig. 5: Infrared spectra A. AR, B.Ni, C. Physical mixture AR: Ni, D. cocrystal AR: Ni (solven evaporation) and E. cocrystal AR-Ni (slurry).

FTIR spectroscopy is widely used to study the chemical and physical structure changes in the molecular structure of a substance. AR has a C-H stretch bands at 2967 cm^{-1} , C=O stretch at 1346 cm^{-1} and O-H bending at 1485 cm^{-1}. NI has a specific secondary amide bands at 3367 cm^{-1}, 2976 and 2639 cm^{-1} which is NH_3^+ bending bands. The loss of the transmission peaks at 2976 and 2639 cm^{-1} referred to NH_3^+ bending bands. Loss of C=O stretch at 1346 cm^{-1} and O-H bending region 1485 cm^{-1} [10,11] showed the presence of hydrogen bonding between AR and NI due to the formation of cocrystals prepared by solvent evaporation method. Cocrystals which were prepared by the slurry method only showed the loss of NH_3^+ group at 2639 cm^{-1}. This suggested that the formation of cocrystals by solvent evaporation method produced more hydrogen bonding than the cocrystals which were prepared by the slurry method.

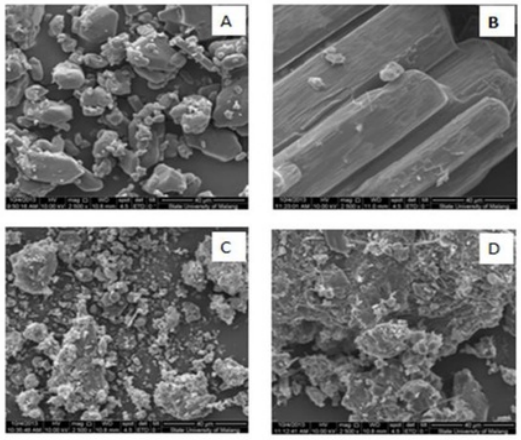

Fig. 6: SEM micrograph A. AR, B. NI, C. AR: NI physical mixture, D. cocrystal AR-NI (solvent evaporation) and E. cocrystal AR: NI (slurry method) with a magnification of 2500X.

Observations using SEM provide visual information about the co-crystal formation compared with the constituent materials [12]. The results showed that the cocrystals prepared by solvent evaporation method produces a more homogeneous aggregate mixture of AR-NI (Figure 6.D), compared with the cocrystal prepared by slurry method. Cocrystal with slurry method still exhibits the long fibers of NI.

CONCLUSIONS

Cocrystal artesunate-nicotinamide was successfully formed using solvent evaporation and slurry methods. This can be proved through their characterization using thermal analysis DTA, powder X-ray diffraction and infrared spectroscopy. The formed cocrystal of AR-NI exhibits different physicochemical characteristics compared to the constituent materials. Cocrystals which were prepared by solvent evaporation method gives a lower energy and is more homogeneous in terms of crystal composition.

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